Original Article

A study of Correlation of Frailty and Cognition in Elderly Individuals

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ABSTRACT

Introduction : Frailty is defined as body's inability to respond adequately to external stressors and a greater risk of adverse outcomes, including disability, hospitalization, institutionalization, and death. A number of studies have shown that frail people are more likely to have dementia or cognitive impairment and that those who already have dementia are more likely to be frail. The purpose of this study was to examine the relationship between frailty and cognition in elderly individuals.

Materials and Methods : It was a Descriptive Cross-sectional hospital based study on subjects of age 60 years and above at Government Medical College, Nagpur during Nov. 2017 to Oct. 2019. A total of 200 subjects were interviewed by a predesigned questionnaire and assessment of frailty was done by Fried's Frailty Index (weakness, slowness, exhaustion, low physical activity, and weight loss). Cognitive score was calculated by MMSE with score of < 24 were cognitively impaired.

Observations and Results : Of total 200 subjects 70% were females and mean age of study population was 68.14 ± 4.66 (S.D) years. 22.5% subjects had cognitive impairment and it was observed that with advancing age the mean MMSE score declined. According to Fried's frailty index 67 (33.5%) were frail, 99 (49.5%) were pre-frail and 34 (17%) were robust. Frail subjects were more cognitively impaired than pre-frail and robust subjects. All components of MMSE were affected in frailty, except Naming. Low BMI, marital status(widowed, divorced and single), economically dependent, weight loss in last 6 months, backache, difficulty in stair climbing and cognitive impairment were predictors of frailty.

Conclusion : Being a part of geriatric syndromes, frailty is also associated with other geriatric syndromes e.g. Cognitive Dysfunction. If frailty is detected earlier in course, some measures can be taken which can be of help to halt or to slow the progression or sometimes to reverse the frailty.

Introduction :

Population ageing is a global phenomenon. It is expected that the proportion of older adults around the globe aged 60 years and older is expected to total 2 billion in 2050, up from 900 million in 2010.[1] The trend clearly reveals that ageing will emerge as a major social challenge in the future; and vast resources will be required towards the support, service, care, and treatment of the elderly persons.[2]

Older age is also characterized by the emergence of several complex health states that tend to occur only later in life and that do not fall into discrete disease categories. These are commonly called geriatric syndromes. They are often the consequence of multiple underlying factors and include frailty, urinary incontinence, falls, delirium and pressure ulcers.[1]

Frailty is characterized by the body's inability to respond adequately to external stressors and a greater risk of adverse outcomes, including disability, hospitalization, institutionalization, and death.[3]

A number of cross-sectional and longitudinal studies have shown that frail people are more likely to have dementia or cognitive impairment and that those who already have dementia are more likely to be frail. This raises important questions about frailty as a potentially modifiable risk factor for dementia and vice versa.[4,5] Frail persons with cognitive impairment were significantly more likely to experience disability and hospitalization events compared to frail non-cognitively impaired subjects.[6]

The precursors to frailty and the associations between frailty and other geriatric syndromes are still relatively unknown. One of these questions is to

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what extent frailty is associated with another geriatric giant, cognitive impairment, and the different domains of cognitive function.

Given the expected growth in the population of older adults in India, it is important to understand the relationship between frailty and health outcomes such as cognition that increase health costs and decrease quality of life. The purpose of this study was to examine the relationship between frailty and cognition in elderly individuals.

Aims and Objectives :

To determine the prevalence of frailty and its association with cognition in elderly individuals.

Materials and Methods :

A hospital based Descriptive Cross-sectional study was performed at Government Medical College, Nagpur over the duration of 2 years (Nov. 2017-Oct. 2019) after the approval from Institute Ethical Committee. The Study subjects of age 60 years and above were selected from accompanying relatives of patients. 200 study subjects were included by calculating the sample size from the prevalence of previous study[9] with 7 percent absolute precision and 95% CI.

Exclusion criteria were physical limitations that would impede the performance of the tests, severe cognitive impairment (MMSE score < 10) and those who were not willing to give informed consent. All the subjects were interviewed with the predesigned Questionnaire and was followed by clinical examination. Evaluation of Instrumental Activities of Daily Living (IADL) was done by Katz Index. Assessment of cognition was done by MMSE and that of frailty was done Fried's Frailty Index.

Katz Index of Independence in Activities of Daily Living : It is a 6-item index that gives an assessment of the performance in the six functions of bathing, dressing, toileting, transferring, continence, and feeding. The scoring of each item of this instrument includes independence (1) and dependence (0). Independence is defined as performing these tasks without supervision, guidance or personal assistance while dependence is defined as doing the tasks with supervision, guidance or personal assistance. The total score is in the range of 0 to 6. The score of 6 represents an independent patient and 0 indicated a very dependent one or total functional disability. The score of 1 to 5 was considered as some functional disability.

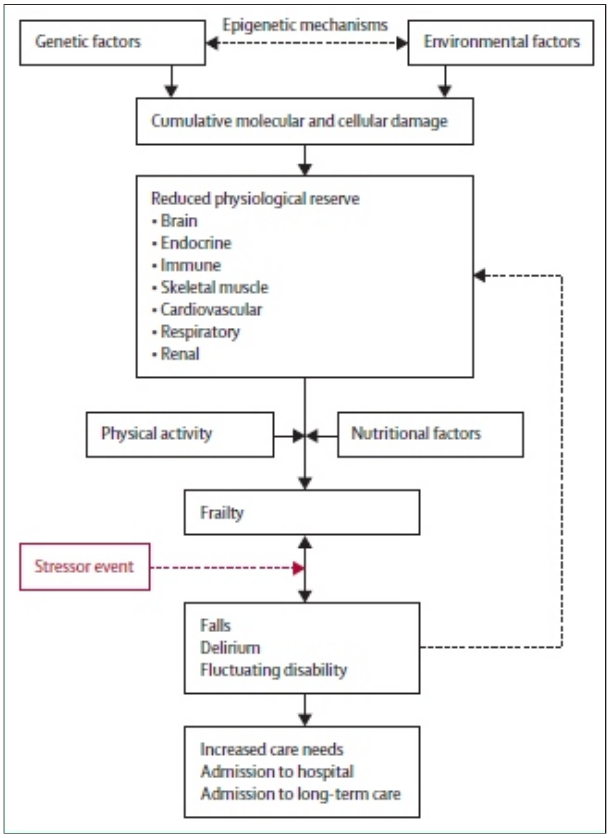

Fig. 1 : **Schematic representation of the pathophysiology of frailty.**

Fried frailty phenotype[12] : A five criteria scale were operationalized as follows :

1. ***Unintentional weight loss :*** ≥ 4.5 kg or 5% of weight loss in the previous year (Self-reported, Yes or No) (OR) BMI ≤ 18.5
2. ***Exhaustion :*** a frequent experience of exhaustion / tiredness (Self-reported, Yes or No)
3. ***Low Physical activity :*** frequency, duration and intensity of usual activities were assessed.

   Frequency of exercise < 5 times a week were considered positive (Self-reported, Yes or No)
4. ***Hand-grip strength (Muscle strength measured by hand dynamometer). Frailty Cut point :***

For Men : [BMI ≤ 24 and GS ≤ 29 kg]; [BMI 24.1-28 and GS ≤ 30 kg]; [BMI > 28 and GS ≤ 32 kg]

For Women : [BMI ≤ 23 and GS ≤ 17]; [BMI 23.1-26 and GS ≤ 17.3 Kg]; [BMI 26.1-29 and GS ≤ 18 kg]; [BMI > 29 and GS ≤ 21 kg]{GS Grip Strength}

5. ***Walking time (time required to walk 15 feet or 4.5 m) was used.***

Frailty Cut point :

In men : [height ≤ 173 cm and time ≥ 7 seconds]; [height > 173 cm and time ≥ 6 seconds].

In women : [height ≤ 159 cm and time ≥ 7 seconds]; [height > 159 cm and time ≥ 6 seconds])

Each criterion was given one point and based on the score an individual is considered Frail : if ≥ 3 criteria present, Pre-Frail : if 1 or 2 criteria present and Robust : 0 criteria present

MMSE is a widely used screening measure of cognitive impairment. It consists of 30 items including orientation, registration, attention, and calculation, recall, language, visual constructions, and the ability to follow simple commands. The MMSE has a maximum score of 30 and a minimum of 0. A score equal to or greater than 24 is taken to indicate no cognitive impairment, whereas a score 19-23 indicates mild, 10-18 moderate and below 10 severe cognitive impairment.[13] HMSE (Hindi Mental State Examination) : Hindi version of the Mini-Mental State Examination was used for illiterate and Hindi speaking population based on the recommendation by *Ganguli et al.* (1995).[14] Cognitive impairment was correlated with Frailty.

Statistical Analysis : Data was entered in MS Excel, coded and analysed in statistical software STATA, version 10.1, 2011. Data analysis included both Descriptive and Inferential statistics. Descriptive statistics were used to summarize quantitative variables with mean, standard deviation (SD), while frequency and percentages were used to summarize categorical (qualitative) variables. Inferential statistics mainly included One way ANOVA and Chi-square test for assessing the significance of the difference in various parameters expressed either as means or proportions in three outcome groups (e.g. Robust, Pre-frailty, and Frailty). Two independent samples (Unpaired t-test) with equal variances were also used for comparing the mean difference in scores in two comparison groups, or sub-groups. The role of baseline characteristics in the association of outcome and other covariates was assessed using Binary Multiple Logistic Regression (MLR) Analysis. Adjusted odds ratios were calculated along with 95% Confidence Intervals and p-values. A p-value < 0.05 was considered statistically significant for all the comparisons.

Observations and Results :

The total number of 200 subjects were included in the study. The mean age of the study population was 68.14 ± 4.66 (S.D) years. The maximum age was 81 years and minimum age was 60 years. The maximum number of study subjects were in the age group of 66-70 years. About 70% were females and only 30% were males. Mean age in females was 67.7 ± 4.37 years and in males was 68.9 ± 5.15 years. About 41.5% of the study population were literate, while 53.5% were illiterate. In the study, 66% were married, 30.5% were widow / widower, 2.5% were divorced and 1% were single. 88.5% study subjects were living with either with their family or spouse while 11.5% were living alone.

24.5% of study subjects were working. The most common addiction in study subjects was tobacco chewing (45.5%) followed by smoking (9.5%) and alcohol consumption (8.5%).

24.5% of study subjects were doing regular exercise or yoga. The most common health problems were decreased appetite (66.5%) followed by difficulty in stair climbing (59.5%) and myalgia (55%). The most common co-morbidities in our study population were systemic hypertension (25%) followed by diabetes mellitus (22%). 13% of study subjects were classified as functionally dependent and 22.5% subjects had cognitive impairment. It was observed that with advancing age the mean MMSE score declined.

of 200 study subjects, 33.5% were frail, 49.5% were pre-frail and 17% were robust. The two main contributors of frailty were poor handgrip strength and slow walking speed. The frailty was significantly associated with the following factors: age, female gender, illiteracy, living alone, economic dependent, current not working. Among the addictions, frailty was associated with tobacco chewing and drinking alcohol. Various health-related factors significantly associated with frailty were: disturbed sleep, decreased appetite, joint pain, myalgia, weight loss in the last 6 months, difficulty in stair climbing, backache and visual impairment. When various co-morbid conditions were studied, no significant association was found with frailty. It was observed that functional dependence was associated with frailty.

Frailty was associated with cognitive dysfunction. Frail subjects were more cognitively impaired than pre-frail and robust subjects. All components of MMSE were affected in frailty, except Naming.

The association of frailty status and various baseline characteristics were analysed using multivariable analysis by logistic regression and it was found that low BMI, marital status (widowed, divorced and single), economically dependent, weight loss in last 6 months, backache, difficulty in stair climbing and cognitive impairment were predictors of frailty.

Table 1 : **Socio-demographic characteristics and health status of participants at baseline according to classification of frailty**

	Total n=200	**Robust n=34**	**Pre-frail n=99**	**Frail n=67**	**P-value**
Age	%	%	%	%	
60-65	27	41.1	24.2	23.9	0.02
66-70	43.5	50	45.4	37.3	
>70	29.5	8.9	30.3	38.8	
Gender					
Male	30	52.9	23.2	23.8	0.006
Female	70	47	73.7	76.1	
Literacy					
Literate	41.5	91.1	68.6	61.1	0.007
Illiterate	53.5	8.9	31.1	38.9	
Marital status					
Married	66	94.1	71.7	43.2	0.001
Others	34	5.9	28.8	56.7	
Living					
Family and spouse	88.5	100	92.2	76.1	0.001
Alone	11.5	0	7.07	23.8	
Economic dependence					
Independent	24.5	61.7	22.2	8.9	0.001
Partial/Pensioner	53	29.4	56.5	59.7	
Complete dependent	22.5	8.8	21.2	31.3	
Current working status					
Not working	75.5	38.2	77.7	91	0.05
Working	24.5	61.7	22.2	9	

Addictions					
Smoking	9.5	8.8	8.08	11.9	0.7
Tobacco	45.5	41.1	44.4	49.2	0.05
Alcohol	8.5	8.8	4.04	14.9	0.048
Exercise					
Regular exercise / Yoga	24.5	44.1	25.5	13.4	0.003
Health problems					
Disturbed Sleep	44	20.5	43.4	56.7	0.003
Decreased appetite	66.5	47.0	66.6	76.1	0.014
Joint pain	51	26.4	46.4	70.1	0.001
Myalgia	53	32.3	49.4	68.6	0.002
Weight loss in 6months	33.5	0	27.2	59.7	0.001
Difficulty in stair climbing	59.5	41.1	53.5	77.6	0.001
Falls in last 6 months	8.5	5.8	11.1	5.9	0.423
Fracture	8.5	0	8.08	13.4	0.071
Seizures	2.5	5.8	1.01	2.9	0.278
Urinary bladder complaint	16.5	11.7	14.1	22.3	0.267
Bowel habits	5.5	0	9.09	2.9	0.248
Backache	40.5	17.6	38.3	55.2	0.001
Visual impairment	41.5	38.2	33.3	55.2	0.018
Hearing impairment	23.5	23.5	25.2	20.9	0.810
Haemorrhoids	16	11.7	15.1	19.4	0.582
Co-morbid conditions					
Diabetes mellitus	22	17.6	19.1	28.3	0.30
Hypertension	25	17.6	24.2	29.8	0.396
IHD	8.5	0.0	12.1	7.4	0.085
COPD	10	11.7	10.1	8.9	0.9
Tuberculosis	6	5.8	4.0	8.9	0.425
Cancer	2	0.0	4.0	0.0	0.125
Katz index					
Functionally independent (Katz score 6)	87	100	97.9	64.1	0.001
Functionally dependent (Katz score < 6)	13	0.0	2.02	35.8	
Cognition					
MMSE $\geq$ 24	87.5	100	96.9	37.3	0.001
MMSE < 24	22.5	0.0	3.03	62.6	

Table 2 : **Various components of MMSE and frailty**

Components of MMSE	ROBUST	PRE-FRAIL	FRAIL	P-value
Orientation to Time	4.68±0.47	4.48±0.50	3.68±0.49	0.001
Orientation to Place	4.82±0.38	4.71±0.45	4.22 ± 0.45	0.001
Registration	2.91±0.28	2.80±0.39	2.61±0.49	0.001
Attention	4.23±0.43	3.89±0.64	2.97±0.71	0.001
Recall	2.57±0.50	2.41±0.49	1.97±0.77	0.001
Naming	1.94±0.23	1.98±0.10	1.92±0.26	0.09
Repetition	0.85±0.35	0.80±0.39	0.59±0.49	0.002
Comprehension	2.94±0.23	2.85±0.35	2.71±0.45	0.008
Reading	0.97±0.17	0.94±0.22	0.85±0.35	0.034
Writing	0.97±0.17	0.94±0.22	0.85±0.35	0.034
Drawing	0.77±0.43	0.69±0.46	0.49±0,50	0.006
Total score	27.64±0.94	26.57±1.48	22.89±1.73	0.001

Table 3 : **Multivariable analysis using binary logistic regression for showing the association between Frailty and various baseline characteristics.**

Variables	Adj. OR	95% CI	p-value	Significance
BMI	3.57	1.64 - 7.69	0.001	S
Marital status	5.26	1.96 - 14.29	0.001	S
Economic dependence	7.14	1.69 - 33.33	0.008	S
Weight loss in last 6 months	7.11	3.19-15.86	0.001	S
Backache	4.08	1.82-9.14	0.001	S
Difficulty in stair climbing	3.31	1.43-7.64	0.005	S
Cognitive impairment	17.48	1.85-164.58	0.012	S

S - Significant

Table 4 : **Age-wise distribution of Cognitive function of study subjects**

	61-65 (n=54)	66-70 (n=87)	>70 (n=59)	P-value
Cognition	%	%	%	
Normal	75.9	85	67.7	0.05
Impaired	24.1	14.9	32.2	
MMSE (Mean ± SD)	25.96±2.23	25.64±2.38	24.8± 2.58	0.05

Discussion :

The frailty was classified according to fried's frailty index and it was observed that 67 (33.5%) were frail, 99 (49.5%) were prefrail, 34 (17%) were robust. In a community-based study on 250 older adults at Pune by *Yashoda Kashikar, et al.* (2016)[9], the prevalence of frailty was 26%. In a community-based study by *Eun Sook Han, et al.* (2013)[15] frailty assessment was done by fried's frailty index and it was found that 9.3% of the respondents were frail, with 42.3% being pre-frail and 48.4% non-frail. In a systematic review and meta-analysis study by *Dhammika D. Siriwardhana, et al.* (2017)[16] the prevalence of frailty varied from 3.9% (China) to 51.4% (Cuba) and prevalence of pre-frailty ranged from 13.4% (Tanzania) to 71.6% (Brazil). The pooled prevalence of frailty was 17.4% (95% CI 14.4% to 20.7%, I2 = 99.2%) and pre-frailty was 49.3% (95% CI 46.4% to 52.2%, I2 = 97.5%). This difference is may be due to different geographical setup, study design, heterogeneity in population in various aspects like culture, life expectancy, education, etc.

In our study, it was found that frail participants were significantly older (69.08 ± 4.96) than prefrail (68.26 ± 4.60) and robust (65.91 ± 3.47) subjects while the same trend was seen in a previous studies[4,5,17]. Among frail subjects 26 (38.8%) were in age group > 70 years, 25 (37.3%) in 66-70 years and 16 (23.8%) in 60-65 years. Aging presents itself to a greater or lesser degree from "successful" aging to "pathological" aging depending on the reserve functions of the different physiological systems, their resilience and the consequent appearance of the disease. Frailty may be considered to reflect an intermediate, but distinct state between these two extremes, where certain reversibility of pathological processes may still exist[18]. This would imply that although aging predisposes to frailty, not all elderly are frail[19] and suggests common, but not identical, pathways between aging and frailty.

The prevalence of frailty was higher in women than men and this finding was consistent with similar previous studies.[4,5,15,17,20] The development of frailty in women is influenced by deficits of various hormones during aging and increased inflammatory states[21]. Also, old Indian females and widowers are less nurtured and less cared for by the family as most of them are economically dependent.

Illiteracy was associated with frailty and it was in accord with the similar previous study[4]. Also, many studies suggested that low education level was associated with frailty[5,15,17]. Explanations for educational differences in frailty may be sought in factors that accelerate the physical aging process, and which are known to play a role in the relationship between educational level and other health characteristics, such as material, biomedical, behavioral, and psychosocial factors[22,23].

In our study married subjects were less frail than the subjects who were single, divorced, widow and widower. and this was consistent with the previous studies.[4,15,17] Being married or living with a partner shows a negative association with frailty; thereby which it lowers the risk of getting frail; this association has an agreement with previous studies[24-27]. Marital status may influence the onset of frailty in older people, since living alone, having little contact with relatives, and limited family care are common features of frail subjects[28]. Married people's health status may be better preserved because they are less exposed to risk behavior, and they have more socioeconomic resources and psychological support.[29] Widowhood appears to increase the risk of disability.[30]

Elderly subjects in our study, who are economically dependent were more frail than those who were economically independent. Poor socioeconomic conditions have an increased prevalence of depression and cognitive impairment.[31] Two kinds of health concerns darken the otherwise bright picture of the well-being of the elderly. First, have medical advances actually increased the frailty of the typical elderly person by prolonging the lives of disabled persons who would otherwise have died? A second, the economic, concern is to what extent costs of long-term care for disabled elderly threaten the economic well-being of the elderly and their children.

It was observed in the study that frail persons were more physically dependent than pre-frail and robust subjects. It was in concert to previous studies.[12,15,17,9] Disability in Activities of Daily Living (ADL), which are the essential activities that a person needs to perform to be able to live independently[54], is an adverse outcome of frailty that places a high burden on frail individuals, care professionals and health care systems[55]. Frail elderly people have a higher risk of ADL disability compared to non-frail elderly people[56]. Effective interventions that prevent disability can diminish the burden caused by frailty.

Among the frail subjects, 42 (62.68%) were cognitively impaired and among pre-frail subjects, 3 (3.03%) were cognitively impaired. Similar relation of the prevalence of cognitive impairment with frailty was seen in the studies given in the following ***Table 1***.

The mean MMSE score was inversely related to frailty. There was a significant association between cognition and frailty. Similar results were observed in previous studies.[133, 135, 145, 183]

Table 5 : **Prevalence of Cognitive impairment with Frailty in various studies.**

Study	Robust %	Pre-frail %	Frail %
Eun Sook Han, et al.[15]			
Male	22.1	32.8	55.8
Female	15.6	21.7	35.2
Monteiro Macuco, et al.[57]	15.6	22.3	38.7
Mariana Asmar Alencar, et al.[17]	6.4	25	58.3
J.M. Jacobs[58]	3.19	7.28	50

A number of cross-sectional and longitudinal studies have shown that frail people are more likely to have dementia or cognitive impairment and that those who already have dementia are more likely to be frail.[5,6,60,61]

Recent studies have identified an association between frailty and subsequent cognitive decline.[58,60,62,63] This raises important questions about frailty as a potentially modifiable risk factor for dementia and vice versa.

From the study, it has been made out that Naming ability was not affected with frailty but all other components of MMSE were affected with frailty. The Rush Memory Aging study found that frailty was associated with a faster rate of decline in cognitive scores across all six domains measured, including memory.[65] Other studies have suggested that memory is less affected than executive function,[57] and consistent with this finding, other prospective studies have shown that frailty is more strongly associated with vascular than Alzheimer's type dementia.[64, 62, 57]

Conclusion :

Of 200 study subjects, 67 (33.5%) were frail, 99 (49.5%) were pre-frail and 34 (17%) were robust. Females were more frail than male subjects. Sociodemographic factors that were associated with frailty were increasing age, female gender, illiteracy, marital status [being widowed, single or divorced], living alone, economically dependent, not working, tobacco chewing and being alcoholic. Health-related factors associated with frailty were disturbed sleep, decreased appetite, joint pain, myalgia, weight loss in the last 6 months, difficulty in stair climbing, backache and visual impairment.

Factors which predicted frailty were, low BMI, widowed, divorced and single individuals, economically dependent subjects, having history of weight loss in the last 6 months, backache, difficulty in stair climbing and cognitive impairment.

It is concluded that frailty is associated with various behavioural and environmental variables. Being a part of geriatric syndromes, frailty is also associated with other geriatric syndromes e.g. Cognitive Dysfunction. If frailty is detected earlier in course, some measures can be taken which can be of help to halt or to slow the progression or sometimes to reverse the frailty.

Future research is needed to better understand the pathophysiological, behavioral, and environmental variables contributing to the relationship between frailty and cognitive decline and to identify new intervention plans designed to improve quality of life and reduce frailty and cognitive disability in older adults.

Limitations of the study :

This being a hospital-based study with convenient sampling it may not represent the general population. Despite these limitations, this study findings, however, provide baseline data and deepen the knowledge of frailty and its assessments.

References :

1. Ageing and health. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health. Accessed November 7, 2019.
2. Central Statisitcs Oiffice. Elderly in India. Minist Stat Program Implementation, Govt India. 2016:1-95. doi:Feb 2016
3. Heuberger RA. The frailty syndrome: A comprehensive review. J Nutr Gerontol Geriatr. 2011. doi:10.1080/21551197.2011.623931
4. Amer MS, El Akkad RM, Hassan HS. Correlation of Frailty Status to Health Related Quality of Life in the Elderly : A Cross - Sectional Study on Community - Dwelling Older Adults Referred to an Outpatient Geriatric Service in Egypt. Middle East J Age Ageing. 2015. doi:10.5742/meaa.2015.92608

5. Robertson DA, Savva GM, Coen RF, Kenny RA. Cognitive Function in the Prefrailty and Frailty Syndrome. J Am Geriatr Soc. 2014. doi:10.1111/jgs.13111
6. Ávila-Funes JA, Amieva H, Barberger-Gateau P, et al. Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: The three-city study. J Am Geriatr Soc. 2009. doi:10.1111/j.1532-5415.2008.02136.x
7. Jotheeswaran AT, Bryce R, Prina M, et al. Frailty and the prediction of dependence and mortality in low- and middle-income countries: A 10/66 population-based cohort study. BMC Med. 2015. doi:10.1186/s12916-015-0378-4
8. Biritwum RB, Minicuci N, Yawson AE, et al. Prevalence of and factors associated with frailty and disability in older adults from China, Ghana, India, Mexico, Russia and South Africa. Maturitas. 2016. doi:10.1016/j.maturitas.2016.05.012
9. Kashikar Y, Nagarkar A. Prevalence and Determinants of Frailty in Older Adults in India. Indian J Gerontol. 2016;30(3).
10. Devkota S, Anderson B, Soiza RL, Myint PK. Prevalence and determinants of frailty and associated comorbidities among older Gurkha welfare pensioners in Nepal. Geriatr Gerontol Int. 2017. doi:10.1111/ggi.13113
11. Iwasaki M, Kimura Y, Sasiwongsaroj K, et al. Association between objectively measured chewing ability and frailty: A cross-sectional study in central Thailand. Geriatr Gerontol Int. 2018. doi:10.1111/ggi.13264
12. Fried LP, Tangen CM, Walston J, et al. Frailty in Older Adults: Evidence for a Phenotype. Journals Gerontol Ser A Biol Sci Med Sci. 2001;56(3):M146-M157. doi:10.1093/gerona/56.3.m146
13. Mungas D. In-office mental status testing: A practical guide. Geriatrics. 1991;46(7):4654-4658.
14. Ganguli M, Ratcliff G, Chandra V, et al. A Hindi version of the MMSE: the development of a cognitive screening instrument for a largely illiterate rural elderly population in India. Int J Geriatr Psychiatry. 1995;10(5):367-377.
15. Han ES, Lee Y, Kim J. Association of cognitive impairment with frailty in community-dwelling older adults. Int Psychogeriatrics. 2014. doi:10.1017/S1041610213001841
16. Siriwardhana DD, Hardoon S, Rait G, Weerasinghe MC, Walters KR. Prevalence of frailty and prefrailty among community-dwelling older adults in low-income and middle-income countries: A systematic review and meta-analysis. BMJ Open. 2018. doi:10.1136/bmjopen-2017-018195
17. Alencar MA, Dias JMD, Figueiredo LC, Dias RC. Frailty and cognitive impairment among community-dwelling elderly. Arq Neuropsiquiatr. 2013. doi:10.1590/0004-282x20130039
18. Bortz WM. A conceptual framework of frailty: a review. Journals Gerontol Ser A Biol Sci Med Sci. 2002;57(5):M283-M288.
19. Schuurmans H, Steverink N, Lindenberg S, Frieswijk N, Slaets JPJ. Old or Frail: What Tells Us More? Journals Gerontol Ser A Biol Sci Med Sci. 2004;59(9):M962-M965. doi:10.1093/gerona/59.9.m962
20. Zhang Q, Guo H, Gu H, Zhao X. Gender-associated factors for frailty and their impact on hospitalization and mortality among community- dwelling older adults: A cross-sectional population-based study. PeerJ. 2018. doi:10.7717/peerj.4326
21. Eichholzer M, Richard A, Walser-Domjan E, Linseisen J, Rohrmann S. Urinary Phytoestrogen Levels and Frailty in Older American Women of the National Health and Nutrition Examination Survey (NHANES) 1999-2002: A Cross-Sectional Study. Ann Nutr Metab. 2013;63(4):269-276. doi:10.1159/000356453
22. Van Lenthe FJ, Schrijvers CTM, Droomers M, Joung IMA, Louwman MJ, Mackenbach JP. Investigating explanations of socio-economic inequalities in health: The Dutch GLOBE study. Eur J Public Health. 2004. doi:10.1093/eurpub/14.1.63
23. Koster A, Bosma H, Broese Van Groenou MI, et al. Explanations of socioeconomic differences in changes in physical function in older adults: Results from the Longitudinal Aging Study Amsterdam. BMC Public Health. 2006. doi:10.1186/1471-2458-6-244
24. Cawthon PM, Marshall LM, Michael Y, et al. Frailty in older men: Prevalence, progression, and relationship with mortality. J Am Geriatr Soc. 2007. doi:10.1111/j.1532-5415.2007.01259.x
25. Pegorari MS, Tavares DM dos S. Factors associated with the frailty syndrome in elderly individuals living in the urban area. Rev Lat Am Enfermagem. 2014. doi:10.1590/0104-1169.0213.2493
26. Chen CY, Wu SC, Chen LJ, Lue BH. The prevalence of subjective frailty and factors associated with frailty in Taiwan. Arch Gerontol Geriatr. 2010. doi:10.1016/s0167-4943(10)70012-1
27. Doba N, Tokuda Y, Goldstein NE, Kushiro T, Hinohara S. A pilot trial to predict frailty syndrome: The Japanese Health Research Volunteer Study. Exp Gerontol. 2012. Doi:10.1016/j.exger.2012.05.016
28. Shanas E. The family as a social support system in old age. Gerontologist. 1979. doi:10.1093/geront/19.2.169
29. Waldron I, Hughes ME, Brooks TL. Marriage protection and marriage selection-prospective evidence for reciprocal effects of marital status and health. Soc Sci Med. 1996. doi:10.1016/0277-9536(95)00347-9
30. Goldman N, Korenman S, Weinstein R. Marital status and health among the elderly. Soc Sci Med. 1995. doi:10.1016/0277-9536(94)00281-W
31. Kumar ND SudhakarTP. Prevalence of cognitive impairment and depression among elderly patients attending the medicine outpatient of a tertiary care hospital in South India. Int J Res Med Sci. 1(4):359-364.
32. Woods NF, LaCroix AZ, Gray SL, et al. Frailty: Emergence and consequences in women aged 65 and older in the Women's Health Initiative observational study. J Am Geriatr Soc. 2005. doi:10.1111/j.1532-5415.2005.53405.x
33. Seematter-Bagnoud L, Spagnoli J, Büla C, Santos-Eggimann B. Alcohol Use and Frailty in Community-Dwelling Older Persons Aged 65 to 70 Years. J frailty aging. 2014;3(1):9-14.
34. Hyde Z, Flicker L, Smith K, et al. Prevalence and incidence of frailty in Aboriginal Australians, and associations with mortality and disability. Maturitas. 2016. Doi:10.1016/j.maturitas.2016.02.013
35. Kojima G, Iliffe S, Jivraj S, Liljas A, Walters K. Does current smoking predict future frailty? The English longitudinal study of ageing. Age Ageing. 2018. doi:10.1093/ageing/afx136
36. Hubbard RE, Searle SD, Mitnitski A, Rockwood K. Effect of smoking on the accumulation of deficits, frailty and survival in older adults: A secondary analysis from the canadian study of health and aging. J Nutr Heal Aging. 2009. doi:10.1007/s12603-009-0085-y
37. Cochen V, Arbus C, Soto ME, et al. Sleep disorders and their impacts on healthy, dependent, and frail older adults. J Nutr Heal Aging. 2009. doi:10.1007/s12603-009-0030-0
38. Ensrud KE, Blackwell TL, Redline S, et al. Sleep Disturbances and Frailty Status in Older Community-Dwelling Men. J Am Geriatr Soc. 2009;57(11):2085-2093. doi:10.1111/j.1532-5415.2009.02490.x

39. Ahmed N, Mandel R, Fain MJ. Frailty: An Emerging Geriatric Syndrome. Am J Med. 2007. doi:10.1016/j.amjmed.2006.10.018
40. Dixit VD, Schaffer EM, Pyle RS, et al. Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by human monocytes and T cells. J Clin Invest. 2004. doi:10.1172/JCI200421134
41. Hermsen LAH, Leone SS, Smalbrugge M, Dekker J, van der Horst HE. Frequency, severity and determinants of functional limitations in older adults with joint pain and comorbidity: Results of a cross-sectional study. Arch Gerontol Geriatr. 2014. Doi:10.1016/j.archger.2014.02.006
42. Landi F, Onder G, Cesari M, et al. Pain management in frail, community-living elderly patients. Arch Intern Med. 2001. doi:10.1001/archinte.161.22.2721
43. Buchman AS, Shah RC, Leurgans SE, Boyle PA, Wilson RS, Bennett DA. Musculoskeletal pain and incident disability in community-dwelling older adults. Arthritis Care Res. 2010. doi:10.1002/acr.20200
44. Morley JE. Anorexia, weight loss, and frailty. J Am Med Dir Assoc. 2010. doi:10.1016/j.jamda.2010.02.005
45. Fougère B, Morley JE. Weight loss is a major cause of frailty. J Nutr Heal Aging. 2017. doi:10.1007/s12603-017-0971-7
46. Verghese J, Wang C, Xue X, Holtzer R. Self-Reported Difficulty in Climbing Up or Down Stairs in Nondisabled Elderly. Arch Phys Med Rehabil. 2008;89(1):100-104. doi:10.1016/j.apmr.2007.08.129
47. Startzell JK, Owens DA, Mulfinger LM, Cavanagh PR. Stair negotiation in older people: A review. J Am Geriatr Soc. 2000. doi:10.1111/j.1532-5415.2000.tb05006.x
48. Lin PC, Hung SH, Liao MH, Sheen SY, Jong SY. Care needs and level of care difficulty related to hip fractures in geriatric populations during the post-discharge transition period. J Nurs Res. 2006. doi:10.1097/01.JNR.0000387584.89468.30
49. Coyle PC, Sions JM, Velasco T, Hicks GE. Older Adults with Chronic Low Back Pain: A Clinical Population Vulnerable to Frailty? J frailty aging. 2015;4(4):188-18890. doi:10.14283/jfa.2015.75
50. Rudy TE, Weiner DK, Lieber SJ, Slaboda J, Boston JR. The impact of chronic low back pain on older adults: A comparative study of patients and controls. Pain. 2007. doi:10.1016/j.pain.2007.01.012
51. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care. Journals Gerontol Ser A Biol Sci Med Sci. 2004. doi:10.1093/gerona/59.3.m255
52. Liljas AEM, Carvalho LA, Papachristou E, et al. Self-reported vision impairment and incident prefrailty and frailty in English community-dwelling older adults: Findings from a 4-year follow-up study. J Epidemiol Community Health. 2017. doi:10.1136/jech-2017-209207
53. Klein BEK, Klein R, Knudtson MD, et al. Relationship of measures of frailty to visual function: The Beaver Dam Eye Study. In: Transactions of the American Ophthalmological Society. ; 2003.
54. Covinsky K. Aging, arthritis, and disability. Arthritis Care Res Off J Am Coll Rheumatol. 2006;55(2):175-176.
55. Rochat S, Cumming RG, Blyth F, et al. Frailty and use of health and community services by community-dwelling older men: The Concord Health And Ageing in Men Project. Age Ageing. 2010. doi:10.1093/ageing/afp257
56. Boyd CM, Xue QL, Simpson CF, Guralnik JM, Fried LP. Frailty, hospitalization, and progression of disability in a cohort of disabled older women. Am J Med. 2005. Doi:10.1016/j.amjmed.2005.01.062
57. Macuco CRM, Batistoni SST, Lopes A, et al. Mini-Mental State Examination performance in frail, pre-frail, and non-frail community dwelling older adults in Ermelino Matarazzo, So Paulo, Brazil. Int Psychogeriatrics. 2012. Doi:10.1017/S1041610212000907
58. Jacobs JM, Cohen A, Ein-Mor E, Maaravi Y, Stessman J. Frailty, cognitive impairment and mortality among the oldest old. J Nutr Heal Aging. 2011. doi:10.1007/s12603-011-0096-3
59. Kim S, Park JL, Hwang HS, Kim YP. Correlation between frailty and cognitive function in non-demented community dwelling older Koreans. Korean J Fam Med. 2014. doi:10.4082/kjfm.2014.35.6.309
60. Buchman AS, Boyle PA, Wilson RS, Tang Y, Bennett DA. Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. Psychosom Med. 2007;69(5):483-489. doi:10.1097/psy.0b013e318068de1d
61. Song X, Mitnitski A, Rockwood K. Nontraditional risk factors combine to predict Alzheimer disease and dementia. Neurology. 2011;77(3):227-234. doi:10.1212/WNL.0b013e318225c6bc
62. Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. Physical frailty is associated with incident mild cognitive impairment in community-based older persons. J Am Geriatr Soc. 2010;58(2):248-255. doi:10.1111/j.1532-5415.2009.02671.x
63. Samper-Ternent R, Al Snih S, Raji MA, Markides KS, Ottenbacher KJ. Relationship between frailty and cognitive decline in older Mexican Americans. J Am Geriatr Soc. 2008. doi:10.1111/j.1532-5415.2008.01947.x
64. Langlois F, Vu TTM, Chassé K, Dupuis G, Kergoat MJ, Bherer L. Benefits of physical exercise training on cognition and quality of life in frail older adults. Journals Gerontol - Ser B Psychol Sci Soc Sci. 2013. doi:10.1093/geronb/gbs069
65. Wilson RS, Barnes LL, Mendes De Leon CF, et al. Depressive symptoms, cognitive decline, and risk of AD in older persons. Neurology. 2002. Doi:10.1212/WNL.59.3.364